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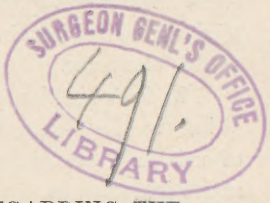

SOME PRACTICAL POINTS REGARDING THE EXCESSIVE EXCRETION OF URIC ACID.*

By C. A. HERTER, M. D.,

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On looking over the records of determinations of uric acid made in my laboratory during the past two years, it occurred to me that it might interest this society to learn what conclusions of a practical nature might be reached from a consideration of these records in their relation to the clinical histories of the cases studied.

The number of individuals in whom the uric-acid excretion was studied is a hundred and sixty-three, and the number of determinations, all made by the Ludwig-Salkowski method, is considerably over six hundred.

From so large a number of observations many statements may be made with positiveness, but, in addition to the conclusions which we may consider to be established beyond doubt, there are others that must be advanced with some reserve and that are to be regarded as suggestions resting on more or less acceptable evidence rather than on established facts. But such suggestions, if carefully con-

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sidered, are often of much value in helping to establish general ideas of a question, and I feel disposed to speak of this, as the subject in point affords considerable material of this character.

The first question that suggests itself for discussion is, What is the significance of the separation in the urine of uric acid or urates? Can any inference be drawn from such separation as to whether uric acid is present in excess or not? This is a question of considerable practical importance, for if the observation of precipitates is of no value whatever, it is high time that this should be generally known. But if, on the other hand, it can be shown that such observation is of value, it is desirable that we should try to fix the range of its use and the nature of its limitations.

The first point to which I would call attention is the fact that we must distinguish between the significance of separated urates and that of separated uric acid. You will pardon me if, in presenting this fact, I remind you of certain things which are well known, in order to make clearer others that are less familiar.

The quantity of uric acid which exists in solution in the urine as free uric acid is so small, if any, that we need scarcely consider it. The uric acid of the urine is present in combination with sodium as urates, or, as Roberts has pretty satisfactorily shown, as quadri-urates—that is, as salts in which a molecule of a bi-urate salt is in loose combination with another molecule of uric acid. The bi-urates do not exist in the urine as such; in fact, they exist nowhere in the body under normal conditions and are only found in the tophi of gout. The separation of the quadri-urates from the urine as amorphous urates is merely a question of solubility. As is well known, a large quantity in a given volume and a low temperature favor this separa-

tion, and it is an important fact that one does not often meet with a separation of urates in a twenty-four-hour sample of urine unless the uric acid is in actual and decided excess. In looking over my records I find that, with very few exceptions, the urines from which the urates had separated contained a greater proportion of uric acid than belongs to health. We come therefore to the conclusion that a deposition of urates in a sample of twenty-four-hour urine is pretty reliable evidence that the uric acid is in excess.

The case is very different with urines in which there has been a separation of uric-acid crystals. While in the case of the urates the separation is dependent merely upon insolubility, in the case of free uric acid the separation depends upon a process of decomposition of the quadri-urates, a fact which has been brought out by Roberts in his recent Croonian lectures. A quantity of amorphous urates—that is, quadri-urates—is carefully prepared from fresh urine and dissolved in distilled water (by heating to boiling and constant stirring). This is set aside for twenty-four hours. During this time a quantity of uric-acid crystals separate and the amount is not increased on further standing. Now, it is a fact of considerable interest that analysis shows the amount of free uric acid in the sediment to be equal to the quantity of uric acid that remains in solution as a urate. The explanation of this is that the amorphous urates, consisting of quadri-urates of sodium, potassium, and calcium, give up one of the two molecules of uric acid of which they are composed, the other molecule remaining in more stable combination with the bases as bi-urates, so that we now have in solution one half the amount of uric acid in combination with the whole of the base present in the quadri-urate. A similar decomposition occurs in the urine itself, but, as the

urine contains many mineral substances in solution, the process is modified and is more complex than in a pure solution. Among the most important of these mineral salts are the phosphates of the alkali metals, which in great degree regulate the reaction of the urine—the urine being acid when monobasic phosphates or monometallic salts preponderate, alkaline when the dibasic phosphates are in excess. The manner in which the uric-acid separation is effected is as follows: First, the water of the urine causes the decomposition of the quadri-urates into uric acid and bi-urates. In this way one half the uric acid is set free, as in the case of the free aqueous solution above mentioned. Now, the bi-urate which remains is at once transformed in the presence of the monobasic phosphates (acid) into a quadri-urate, for by a double decomposition two atoms of bi-urate with one of acid phosphate change into one molecule of quadri-urate and one of dimetallic phosphate as follows:

$$\underset{\text{Bi-urate.}}{2\,(M\bar{U}_2)} + \underset{\text{Monometallic phosphate.}}{(MHPO_4)} = \underset{\text{Quadri-urate.}}{(M\bar{U}_4)} + \underset{\text{Dimetallic phosphate.}}{(M_2HPO_4)}$$

This process of decomposition and recomposition goes on in an acid urine until all the uric acid has been liberated.

From what has just been said, it is clear that the acidity of the urine is an important factor in determining the deposition of uric acid. In fact, every acid urine, if protected against putrefaction, will deposit most of its uric acid in the course of time. The rapidity of the deposition, of course, varies greatly, but every acid urine has a tendency to deposit its uric acid. Certain influences are, however, at work to inhibit and delay this liberation. Important among these influences is that of the saline constituents of the urine, especially the neutral dipotassic phosphates,

which in very small amounts have a pronounced inhibitory action. Another influence of importance is that of the coloring matter. Urines rich in coloring matters deposit their uric acid more slowly, other conditions being similar, than those which are light in color; and urines deprived of their coloring matter by filtration through animal charcoal show a much more rapid decomposition of the quadriurates than before filtration. We must thus recognize numerous influences at work in determining the precipitation of uric acid—influences which we must admit to be only imperfectly understood, but among which it seems fair to regard the factor of acidity as the most important. It requires no argument to show the important bearing of these conditions upon the formation of uric-acid calculi, but this is a subject aside from the present line of inquiry. What chiefly concerns us here is the fact that in many urines which contain no excess of uric acid a sediment is formed soon after or even before the urine leaves the bladder. Of course, urines that contain a large amount of uric acid per unit volume are more liable to deposit a uric-acid sediment than urine containing a smaller amount, everything else being equal. But the point to be emphasized is that other influences are so great that the difference in the amount of uric acid present has little to do in deciding the result. I noted with interest, on looking over my records, the circumstance that of the urines in which uric acid was deposited soon after the bladder was emptied, there were many more urines in which the uric-acid content was normal than in which it was excessive. We may therefore come to the two following conclusions without much hesitation:

1. That a urine from which there is an early separation of uric acid gives us no real reason to think that the actual content of uric acid is excessive.

2. That a urine from which the urates separate gives us good reason to believe that there is an actual excess of uric acid, and that this probability is increased if the density of the urine is less than 1·025.

Unfortunately, the converse of the latter statement is not true; we can not conclude from the circumstance that a urine does not deposit its urates that it does not contain too much uric acid. How far this is from being true is shown by the fact that a very large majority (more than three quarters) of all the urines with excessive uric acid of which I have records did not deposit their urates.

In speaking of an excessive or normal excretion of uric acid, it has been assumed that we possess a standard for comparison on which reliance can be placed. This standard is the ratio of the uric acid excreted in the twenty-four hours to the urea excreted in the twenty-four hours. As already pointed out elsewhere, the ratio of uric acid to urea, in a healthy adult upon a mixed diet, varies little from day to day. In different individuals the fluctuations in health are considerably wider, but not so wide as one might expect. The statement was made by me a year ago that the normal ratios had been found to vary from 1 to 45 to 1 to 55 or 60. Since then many more individuals have been studied, and it may be safely stated on the strength of this experience that the normal ratio is expressed by these figures. In most healthy individuals the proportion is not far from 1 to 50. Instances certainly occur in which the ratio averages somewhat higher than 1 to 45 in persons whose health is apparently of the best, but this is so exceptional that we need scarcely take account of it. Whenever the ratios of an individual average higher than 1 to 40 we are justified in regarding this case as one in which an excess of uric acid is being excreted. Whenever the ratio runs higher than 1 to 35 the excess of uric acid is

to be considered large. I have never met with continuous ratios so high as this except in persons whose health was distinctly impaired. A proportion of uric acid to urea higher than 1 to 30 indicates very great excess of uric acid, and is only rarely observed. A ratio higher than 1 to 20 I have never found.

I wish now to ask your attention for a few minutes to some points regarding the clinical and pathological significance of excessive uric acid excretion. This subject is, to my mind, more interesting than any other connected with the uric-acid problem—far more interesting, for example, than the purely chemical considerations that refer to the separation of uric acid from the urine.

The first point of general interest which I should like to emphasize is what may almost be called the universality of uric-acid excess in functional disease. I know of nothing in connection with my work upon this subject that caused me greater surprise than the constantly increasing category of maladies in which too much uric acid was found. It is not my intention to consider here in detail the individual morbid states that are associated with too great an output of uric acid, but rather to touch upon the distribution of these states in their wider relation to the subject under consideration. It is convenient to group the cases in which too great an output of uric acid is found in two general classes, the first comprising those cases where the excess is of continuous occurrence, the second those where the excess is of transient duration. In the first category are to be found, in my experience, every case with pronounced neurasthenic symptoms, most cases of simple anæmia, probably most blood diseases, certainly leucæmia, most cases of chronic gastric dyspepsia, most cases of chronic intestinal indigestion, cases of *petit mal*, many cases of chronic nephritis, many cases of phthisis,

and chronic febrile states generally. This list might be extended almost indefinitely, but the extension would serve to confuse the subject rather than clear it. For example, most phthisical patients excrete a good deal more uric acid than they ought, but it is not at all clear that this excess is related to the tubercular process in the lung; it is far more likely that the excess depends upon the fever, or upon the digestive derangements, or upon the associated anæmia. Similarly, in cases of chronic nephritis it is more than probable that the increased output is related to the accompanying anæmia. It would certainly do much to clarify our understanding upon this subject if it could be shown that in all these apparently varied conditions there is a single underlying condition to which the increased output of uric acid might be referred. There are, indeed, some facts to which I shall later make reference, which suggest the view that the excessive uric acid elimination usually bears a definite relation to a state of leucocytosis, but, unfortunately, we are not in a position to more than hint at the possibility of this being so. We must content ourselves for the present with the knowledge that anæmia is one of the important associations, or causes, if you prefer, of excessive uric-acid output, and that this may be at the bottom of a large proportion of the chronic states we are considering. I have been surprised to find how many neurasthenics whom there was no reason to think anæmic have shown a decidedly reduced proportion of hæmoglobin. But while it is possible that we should refer to anæmia the excess of uric acid in some neurasthenics, it is more likely that in most of these cases the excess depends upon the associated disorders of digestion.

The conditions in which there is a transient excess in the output of uric acid are varied. Any acute disorder of gastric or intestinal digestion appears sufficient to increase

temporarily the elimination of uric acid. A very large meal often increases considerably the relative output of uric acid for twelve, twenty-four, or thirty-six hours in a perfectly normal individual and without giving rise to any appreciable disorder of digestion. The use of a considerable quantity of alcohol has the same effect, which is especially pronounced in the case of wines that contain much sugar. The effect of a large amount of sugar (eight to sixteen ounces of saccharose a day) is apparently to increase uric-acid excretion. It is important to note here that the influences just mentioned are much more operative in producing an excessive output of uric acid in persons whose uric acid is habitually a little in excess than in persons who are quite normal in their output. Other conditions that are associated with a temporary increase of the uric-acid output are the following: Almost any form of functional headache, including the migraine paroxysm, and seizures of *grand mal* (the increase being present in these cases on the first or second day after the seizure).

The occurrence of excessive uric-acid elimination in so many apparently different conditions leads one to inquire whether these conditions have any clinical feature in common through which they may be related to the uric-acid excess. Apparently, all that can be said in this connection is that all, or nearly all, the states which are characterized by uric-acid excess are associated with signs of some disturbance of general nutrition, and it may be said, in general, that the greater the excess the more pronounced are the evidences of nutritive disorder. We are not yet in a position to assert that the converse of this holds good—that all, or nearly all, disturbances of nutrition are accompanied by an increased uric-acid output—yet I can not but suspect that a very great extension of our observations would lead to the view that there are few derangements of nutrition,

whether transient or prolonged, which fail to exhibit some degree of this excess. If we accept this view of the clinical meaning of uric-acid excess, it is clear that this conception must modify not a little some of the currently accepted notions, one might almost say prejudices, upon this subject. It becomes necessary to do away entirely with the idea that uric-acid excess is related specifically to any particular clinical state, and it leads us to inquire into our use of certain current expressions which have originated in misconceptions and have been passed on from writer to writer. After what has been said, it requires no argument to show that the expression "uric-acid diathesis" is one that should be used as little as possible, or, if used at all, should be used with a clear understanding of the vagueness of the term. What right have we to speak of a "uric-acid diathesis" as a condition in any way distinctive, when we know that an excessive output of uric acid is merely one of the expressions of a great variety of nutritional disturbances? What can be meant by the expression more than such excessive elimination continued for a considerable period of time? The word diathesis in this connection is deprived of any special meaning, and, to my understanding, had better be used for clinical states having more fixed characters if it is to retain any meaning at all. Another expression which appears to me objectionable is "lithæmia," as ordinarily employed for designating the excess of uric acid in the urine which is construed to mean an excess of uric acid in the blood. For we have seen that uric-acid crystals may separate in the urine when there is no excess whatever of uric acid, and may not separate when there is an excess. When uric-acid crystals separate in the urine soon after it is passed, we may assume that there is some disorder of nutrition back of this separation, which gives rise to it by causing too acid a urine, or one in which

the salts or other constituents of the urine are defective. But, while these deviations in composition are surely abnormal, they must be sharply distinguished from the real excess of uric acid which the proper use of the word lithæmia implies. It is better to admit our ignorance of the real nature of these disturbances, and speak merely of an excessively acid urine with separation of uric acid, or of a deposit of urates, than to mask our ignorance with a euphemism like "lithæmia." If we have reason to suspect that the blood actually contains too much uric acid, let us make use of the term "uric acidæmia," suggested by von Jaksch.

Before speaking of the diagnostic and prognostic significance of an excessive uric-acid output, or of the treatment that appears best adapted to it, I should like to make brief reference to certain general physiological and pathological considerations. In the first place, the idea that uric acid is formed in excess in consequence of defective oxidation must be regarded as having no good foundation, although it is a current view. Senator, and also Naunyn and Riess, found that there was no distinct increase in uric acid in dogs in which dyspnœa had been experimentally produced. Bunge, working much more recently, found the uric-acid output in patients with respiratory disease to vary within the normal limits. The idea that uric acid is a product which is in process of becoming urea is part of the suboxidation theory and must fall with it. Of course it is easy to see how, upon paper, the oxidation of solutions of uric acid may be converted into one of urea, but, unfortunately, there is no evidence that this really occurs in the body. Then, again, the view that uric acid is formed by the activity of the renal epithelium must be regarded as mere hypothesis. It is, in fact, one of those opinions that are based merely upon a more or less skillful juggling with

chemical possibilities that are suggested by the contemplation of formulæ, unsupported by experimental evidence. Those who formulated this opinion did indeed make use of the supposition that the blood never contains any uric acid. "How is it," said they, "that the blood contains no uric acid if this uric acid is really formed anywhere else in the body than in the kidney?" This view of the problem is, however, upset by the fact that von Jaksch and others have found uric acid in the blood in anæmia and other conditions in appreciable quantities. The reason it is found in health in extremely small quantities only is probably because the small quantity formed is very rapidly eliminated by the kidneys. That the renal epithelium can have little or nothing to do with the formation of uric acid is further shown by the experiments of Schröder, who found that in birds from which the kidneys had been taken uric acid continued present in the blood and accumulated in the liver. The balance of evidence at the present time is strongly in favor of the view that uric acid is formed to a large extent both in the liver and spleen.

Have we any hypothesis as to the significance of uric acid which will take the place of the views which modern research has overturned? Considerable evidence has been accumulated which goes to the support of a hypothesis which is essentially modern and is of general biological interest. It is this: that most or all the uric acid which is excreted is derived from the nuclein in the nuclei of cells throughout the body—especially, according to some, the white blood cells—from the breaking down of these nuclei. As this view is one which is gaining ground and has considerable practical importance, we may briefly review the evidence on which it is based. Much of this evidence has been collected by Horbaczewski in a recent publication. In the first place, it was found that if the pulp of spleen be

allowed to commence putrefaction by digesting it for eight hours at a temperature of 50°, the extract obtained yielded xanthine or hypoxanthine on simply boiling. If the digestion was carried further with fresh blood, uric acid was obtained in considerable quantities, 2·5 milligrammes of uric acid having been got from one gramme of the splenic pulp. Further, when the nuclein separated from the splenic pulp undergoes digestion with fresh blood, uric acid is formed. These experiments are very properly interpreted as showing that uric acid, with its allied leucomaines, xanthine and hypoxanthine, can be obtained by the destructive transformation of nuclein. The other tissues of the body, excepting tendons, may be caused to yield uric acid by similar processes, but it is from the white cells of the blood that the major part is derived. This is thought to be shown by the following facts—namely, that conditions which increase the number of white cells in the blood, and consequently stimulate their destruction as well as formation, coincidently increase the output of uric acid. If this shall be shown to be true, it will certainly be a strong support to the hypothesis. It is claimed by some that this has already been satisfactorily demonstrated, but we may be pardoned for expressing some caution in accepting this statement, as the evidence that exists appears to us in several respects imperfect.

In detail, the following facts are brought forward to support the above view: If rabbits or starving men are fed on nuclein from spleen pulp, the uric acid elimination is greatly increased. This fact appears hardly to possess the value as evidence attributed to it by Horbaczewski, and does not necessarily show that the uric acid is derived from nuclein, since many substances that derange nutrition could doubtless be shown to have a similar effect. It is claimed further that a marked leucocytosis is induced by the use of

nuclein taken by the stomach or hypodermically. Again, when you produce a physiological leucocytosis by giving large amounts of nitrogenous food, there is observed an increase in uric acid; and when this physiological leucocytosis is reduced by diminishing the nitrogenous food, there is a corresponding reduction in the excretion of uric acid. Further, it is broadly held, though I fear with insufficient reason, that drugs which increase leucocytosis, coincidently increase uric-acid excretion, and, conversely, that drugs which diminish the number of white cells in the blood decrease the uric-acid output. Another fact which is advanced with a view to strengthening the hypothesis of a relation between leucocytosis and uric acid is that the excretion of uric acid is habitually greatest at the time when the blood contains the greatest number of leucocytes—that is, from two to three hours after a meal.

In view of the foregoing evidence, I think we may accept the nuclein view of the origin of uric acid as a working hypothesis, though we require a considerable accession of evidence, including the evidence to be obtained from the study of uric acid in birds and snakes (in which uric acid takes the place of urea), to enable us to accept it as a theory. Since, according to this hypothesis, the formation of uric acid has its origin in a chemico-physical process of such universality as the breaking down of the nuclei of cells, it is not difficult to understand the clinical fact that many different conditions are capable of modifying the output of uric acid, the diverse influences becoming operative through the same biological process.

And now, having tried to obtain some insight into the physiological nature of the increased uric-acid output, we may return to the more practical question, What is the actual value, in practice, of our exact knowledge of the uric-acid output of our patients? In the first place, it appears

to me that the value of this knowledge is quite different from what it is popularly supposed. It does not give us information about a particular morbid state or diathesis, but rather an indication of the existence of a defect in general nutrition with little or no information as to the nature of this defect, except that it can be induced, and is perhaps generally induced, by the existence in the blood of a toxic substance formed during the process of digestion.

Now, this information, general as it is, has this value in practice: It gives us an objective basis for deciding whether the line of treatment that is being pursued is or is not effective. Thus, if I find that a patient has a habitual ratio of uric acid to urea of 1 to 25, I know from experience with such cases that he has a disturbance of nutrition from which it is doubtful if he will recover under any treatment, unless the disturbance from which he is suffering be an acute one. If I find the relative ratio to be 1 to 40 or 1 to 35 (on a mixed diet without alcohol), I consider that I have to deal with a distinct but not extreme excess of uric acid which will be lessened and perhaps entirely removed by treatment. Moreover, these results upon the uric-acid output, being very accurate, give us a criterion of judgment which we may employ separately from the symptoms themselves. Again, if a patient with excessive uric acid be put upon treatment calculated to remove the primary trouble and hence reduce the excess, an examination of the urine in two weeks from the beginning of treatment shows conclusively whether this treatment is having the desired effect or not. There is thus little delay in determining whether the treatment is or is not satisfactory. If the urine shows no improvement, it is conclusive evidence that the treatment is not effective and must be changed. There is another prognostic point which I should emphasize here. The fact that the uric acid returns to normal upon a careful diet

does not necessarily show that the real trouble is removed or that the patient has recovered, for mere dieting will reduce the output very much. The crucial test is to put the patient on a reasonable mixed diet. If on such a diet the uric acid remains normal, we may assume that the nutritive disorder on which the excess depended has been improved. If, however, the uric acid runs up, we know that the improvement was only apparent and due merely to the continuance of a restricted diet. In conclusion, therefore, we may say that the chief value of determining uric acid in disease is the light it gives us upon prognosis and upon the intelligent conduct of treatment. Its value in diagnosis is much less, and has, I believe, been greatly exaggerated through the idea that uric-acid excess indicates a special condition. I have met with a few cases where uric acid was eliminated in excess without there being symptoms to correspond; but this is certainly rare, and, generally speaking, it is not very difficult to predict from the symptoms in what cases such excess is likely to be found. This fact leads me to think that a good deal too much importance is attached to obtaining an exact uric-acid method for the use of physicians. The number of cases where it is important to have exact knowledge of the uric-acid output does not appear to be very large, and it is hardly worth the effort of the physician to learn an exact method for occasional use. It is better, I think, to send the urine for examination to a reliable commercial chemist, who can do the Ludwig-Salkowski method, and report the results for the interpretation of the physician.

There is one aspect of the elimination of too much uric acid about which we have no knowledge whatever at the present time, and that is the effect upon the kidney of habitually excreting this excess. There are those who see in the existence of general arterio-sclerosis and chronic

diffuse nephritis evidence of the long-continued activity of some toxic substance in the blood, and it has been suggested and even affirmed that uric acid is this substance. It would certainly be interesting to follow the history of persons who habitually excrete too much uric acid, with an eye to renal sequelæ; but it must be candidly owned that we have not very much reason to be suspicious of uric acid as a poison. So far as known, people who are very anæmic for a long period or very neurasthenic are not more liable to kidney disease than others, yet we know that they are among the most inveterate uric-acid offenders. While upon the most purely theoretical grounds it does not seem very likely that uric acid has much to do with chronic nephritis, it appears to me that an experimental research might with advantage be undertaken into the possible relation between uric acid and other nitrogenous extractives and the causation of chronic diffuse nephritis and its associations.

When we come to the question of treatment it becomes especially important to bear clearly in mind what I may call the central facts of this paper—that an increase of uric acid does not mean that the patient is suffering from the effects of an excessive quantity of uric acid in the blood; that he is suffering not from disturbance in the later stages of metabolism, but rather from some primary disturbance of which the exact nature is at present unknown in the earlier stages of assimilation and absorption, this disturbance (whether or not the same in all cases) being associated with a great variety of clinical manifestations. As a rule, there are more or less evident errors of digestion, and it is to these that treatment should be especially addressed, though as yet we do not know enough about the variations in the intimate nature of these primary disorders to enable us to individualize closely in our treatment. There are,

however, certain facts of a hygienic nature that seem to be generally applicable. Diet stands first in order among such means. Speaking generally, a diet consisting chiefly of animal nitrogenous food is that which best suits most uric-acid offenders. My practice in prescribing a diet is this: An effort is made to "size up" the case as to gravity from previous experience, and a diet is ordered consisting chiefly of milk, red meat, green vegetables, and zwieback, starches and sugar being diminished or cut off according to the indications. It is best at first to make only a moderate reduction, if possible, in the carbohydrates. If at the end of two weeks the uric-acid ratio is found to lie in the neighborhood of 1 to 50, the diet is considered satisfactory, and as much carbohydrate food is added, in the form of rice, hominy, and potatoes, as is consistent with keeping the ratio in this vicinity. It is a very easy matter to simply reduce the uric-acid ratio without any regard for other considerations; you can do it by putting your patient on a milk diet or on a Salisbury diet. But it is usually a mistake to do this without regard for the weight of the patient, which is greatly reduced by such a course and which it becomes exceedingly difficult to restore. I believe that the wisest plan is to keep patients on a mixed diet, in which all classes of food are represented, and to allow just as much starchy food as is consistent with the avoidance of a uric acid excess. I believe there are persons who consider the use of red meat injurious in these cases and who prefer to put their patients on a wholly or largely vegetable diet. I have never had the hardihood to order a vegetable diet for purposes of treatment, but I have used such a diet for experimental purposes and found that there was induced not only intestinal disturbances but a higher uric-acid ratio than had been present when a mixed diet with free use of meat was allowed. Another point in regard to diet is the

avoidance of an excess of nitrogenous food. Because an animal nitrogenous food is well borne, we are not justified in pushing it to excess, as is often done with a view to "building up" patients. Such an excess may be borne for a time and even appear to do good, but after a while it gives rise to digestive disturbances. A good rule is not to let the amount of urea excreted go beyond, say, one gramme in the twenty-four hours to five pounds' weight of the patient. Thus a person weighing a hundred and fifty pounds would be allowed to excrete in the neighborhood of thirty grammes of urea daily, while a person weighing a hundred pounds would be allowed to run as high as twenty grammes. In this calculation the weight is considered as undergoing little alteration.

The influence of overfatigue is, I believe, very great in bringing about the primary disorder of absorption which leads to uric-acid excess. I have repeatedly had the experience of seeing a uric acid run up in consequence of physical overexertion while a restricted diet was being rigidly adhered to, and can not but feel that the avoidance of such excessive fatigue is one of the most important things in the treatment of these cases. The endurance of these patients is not usually great and each has to learn for himself how much and how little he may safely do. There are many persons whose daily duties, though of a sedentary nature, are largely fatiguing and who become further exhausted by active exercise. It is in cases of this sort that massage has seemed to me to be particularly beneficial in developing the power of resistance to fatigue. In some cases, where exercise was at first impracticable, endurance was so increased after a few weeks of massage that active exercise in walking could be recommenced without fatigue. It has seemed to me that in business men the effects of massage have been distinctly better

when the treatment was applied in the morning before business than in the afternoon or evening.

Of treatment by drugs I have little to say, as such treatment appears to me quite secondary in importance to more purely hygienic measures. But while treatment by drugs is of secondary influence it should not be overlooked, for it may be a real help. Of all drugs, arsenic appears to be the most valuable in aiding nutrition to overcome the disturbances which result in uric-acid excess. How it acts is not really clear, but there is no doubt in my mind of its ability to modify nutrition in such a way as to reduce an excessive output of uric acid. The most striking proof of this I have met in cases of chorea, in which the symptoms and the associated large excess in uric acid have been proportionately controlled by arsenic. Where anæmia exists it is well to give iron and arsenic alternately.

A good deal has been said about the use of drugs that are supposed to "wash the uric acid out of the system." Alkaline waters, lithia water, and of late piperazine water have been recommended for this purpose. When we reflect that uric acid is eliminated with great rapidity as soon as it gets in the blood, and that it is itself no poison, it is difficult to see how we can do good by attempts to eliminate it. The trouble is at the other end of the process, and we should try to check uric-acid formation instead of resorting to the ridiculous attempt to eliminate what does no harm and eliminates itself. The "washing-out" treatment always reminds me of the good woman whose child was run over, but who was greatly consoled by the thought that the brute of a driver had been arrested. The damage is done, and the deed is a thing of the past when the excess of uric acid gets into the blood; there is not even the motive of revenge for trying to eliminate it. Then, again, it is extremely doubtful whether these lauded drugs really do "eliminate." I

can not make any positive statement about lithia, but I have experimented with piperazine on normal and abnormal persons and have satisfied myself that it has very little effect on uric-acid excretion. A trivial increase in uric acid was indeed noted, but this was attributable to the slight disorders of digestion induced. In a considerable number of the persons who excrete too much uric acid the urine is scanty and of high specific gravity, and the free use of water helps to restore the proper volume and density of the urine. It seems more than probable that the various mineral waters recommended for the so-called uric-acid diathesis do good as diuretics rather than through any influence upon the formation or elimination of uric acid. I may take this occasion to say that while piperazine has no appreciable effect upon uric-acid formation or elimination, it has seemed in one case of gravel to reduce very much the size of the calculi passed and to diminish the frequency of the attacks.

To conclude, it appears to me that we have been attaching a false significance to uric acid in its relation to disease. The view that uric acid is in any sense a factor in disease, except in a purely mechanical way, is, I believe, destined to die out wholly. We have been attributing to the ash the qualities of the flame.